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Dr. Christine Augustyniak
U.S. National Coordinator for the
OECD Test Guidelines Program
U.S. Environmental Protection Agency
Ariel Rios Building, Mail Code 7509P
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Dear Dr. Augustyniak:

On behalf of the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM), we are pleased to provide the enclosed draft of a new OECD Guidance Document (GD) on *Using Cytotoxicity Tests to Estimate Starting Doses for Acute Oral Systemic Toxicity Tests*. The proposed Guidance Document is based on the National Toxicology Program (NTP) Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM) and European Centre for the Validation of Alternative Methods (ECVAM) co-sponsored international, multi-laboratory validation study of two *in vitro* cytotoxicity test methods (see the NICEATM/ECVAM Validation Study of In Vitro Cytotoxicity Test Methods at http://iccvam.niehs.nih.gov/methods/acutetox/inv_nru_announce.htm), as well as a technical evaluation and international independent peer review (see 2006 Peer Review Panel Report at http://iccvam.niehs.nih.gov/methods/acutetox/inv_nru_speerrev.htm). We are submitting this proposed Guidance Document pursuant to our submission of an OECD Standard Project Submission Form (SPSF) to OECD through Dr. Jerry Smrcek of the U.S. EPA on January 30, 2009. We ask that you forward this document expeditiously to the OECD Secretariat for consideration by the member countries.

ICCVAM considered recommendations from an international, independent expert review panel and from ICCVAM's advisory committee, the Scientific Advisory Committee on Alternative Toxicological Methods (SACATM), as well as public comments received during the review process in making its recommendations on the use of the *in vitro* test methods (see the ICCVAM Test Method Evaluation Report for the *in vitro* cytotoxicity test methods at http://iccvam.niehs.nih.gov/methods/acutetox/inv_nru_tmer.htm). ICCVAM concluded that the 3T3 and NHK NRU test methods are not sufficiently accurate to predict acute oral

systemic toxicity for the purpose of regulatory hazard classification. However, ICCVAM subsequently recommended that the two *in vitro* cytotoxicity test methods may be used in a weight-of-evidence approach to determine the starting dose for the current acute oral systemic toxicity protocols (i.e., the Up-and-Down Procedure [UDP], the Acute Toxic Class [ATC] method) which are described in OECD test guidelines 423 and 425. Data from the cell-based tests can then be used to identify the most appropriate starting dose to test in animals. For non-toxic substances estimated to be nontoxic, the *in vitro* methods can reduce the number of animals required for each *in vivo* test by as much as 50%. To facilitate the greatest reduction in animal use, ICCVAM proposes to incorporate these recommendations on the use of these test methods in the proposed Guidance Document to encourage their use by OECD member countries.

If it is determined that an Expert Consultation meeting is necessary based on the results of the commenting round by member countries, NICEATM-ICCVAM would be glad to organize and host such a meeting and provide all necessary administrative and logistical support for this meeting.

We believe that the adoption of the proposed Guidance Document will support further reduction and refinement of animal use for acute oral toxicity testing. Please feel free to contact us at any time if you have questions about the proposed document.

Sincerely,

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Enclosures